AF/1645

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First Named	S. Loosmore
Group Art Unit	1645
Examiner Name	J. Hines
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ENCLOSURES *(check all that apply)*

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Signature	
Date	October 19, 2001

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	S. Loosmore, et al.
Appl'n. No.	:	09/210,995
Filed	:	December 15, 1998
Title	:	MULTI-COMPONENT VACCINE COMPRISING AT LEAST TWO ANTIGENS FROM HAEMPHILUS INFLUENZAE TO PROTECT AGAINST DISEASE
Grp./A.U.	:	1645
Examiner	:	J. Hines
Docket No.	:	1038-844 MIS:jb

October 19, 2001

BY COURIER

The Commissioner of Patents
and Trademarks,
Box AF
Washington, D.C. 20231,
U.S.A.

REPLY BRIEF UNDER 37 CFR 1.193 (b)(1)

Sir:

This Reply Brief is submitted in triplicate in response to the Examiner's Answer dated August 21, 2001. A second Amendment after Final Action is being submitted simultaneously herewith, cancelling claims 1 to 5, to narrow the issues for appeal and to focus the argument on the specific combination of antigens specified in claim 6. The following discussion is on the basis that such Amendment is entered.

The Examiner maintained rejection of claims 1 to 24 under 35 USC 103(a) as being unpatentable over Barenkamp (WO 97/36914) in view of Loosmore et al (USP 5,506,139). Since the Examiner's position with respect to the disclosures of the prior art appears to have been modified in certain respects from that stated in Final Action, some further comment on the obviousness rejection is required.

Before turning the Examiner's discussion of the prior art as set forth in the Examiner's Reply, it is noted that, while, indicating that Applicants Amendment after Final dated October 13, 2000 had been filed, it would not appear that the

Amendment has been acted on and entered. The Examiner simply states in the Answer:

"Claim 22 has been amended subsequent to the final rejection."

This statement implies that the Amendment has been entered but no specific Advisory Action has been received in this regard.

Referring now to the prior art rejection, as noted in our Appeal Brief, applicants invention is directed to an immunogenic composition for conferring protection in a host against disease caused by *Haemophilus influenzae*, including otitis media. The composition comprises at least two different antigens of *Haemophilus influenzae*, at least one of the antigens is an adhesin and, as recited in claim 6, is a high molecular weight (HMW) protein of a strain of non-typeable *Haemophilus influenzae* and the other of the antigens is not an adhesin and, as recited in claim 6, is an analog of *Haemophilus influenzae* Hin47 protein having a decreased protease activity, which is less than about 10% of that of natural Hin47 protein.

It is undisputed by applicants that Barenkamp WO 97/36914 (and its corresponding US Patent No. 5,977,336) discloses the high molecular weight (HMW protein of non-typeable *Haemophilus influenzae* and that this protein is an adhesin. It is further undisputed by applicants that Loosmore et al (USP 5,506,139) discloses an analog of *Haemophilus influenzae* Hin47 with reduced protease activity and that this protein is not an adhesin. It is applicants position that the cited prior art contains no suggestion to combine the two antigens in an immunogenic composition and that the prior art further lacks any motivation to select these <u>specific</u> proteins for incorporation into an immunogenic composition.

In discussing the Barenkamp reference, the Examiner indicates, as discussed in the Brief, that Barenkamp contain the statement on page 7, lines 1 to 5, that the immunogenic composition described in Barenkamp may also comprise at least one other immunogenic or immunostimulating material and at least one adjuvant. This passage contains no specific teaching to combine the mutant Hin47 protein with HMW protein in an immunogenic composition. There is no suggestion at all in this passage that the other immunogenic material should be from *H. influenzae*.

The Examiner repeats the fallacy that:

> "Barenkamp et al (WO 97/36914), teach complexing additional components to the antigenic composition to enhance immune response including herpes simplex virus vaccine, pseudorabies virus vaccine, tetanus toxoid, poliomyelitis virus vaccine, hepatitis B virus antigen and others (pages 24-25, lines 7-10)."

As has been repeatedly pointed out, most recently in the Brief, this is an incorrect statement. As has been repeatedly pointed out, the references to herpes simplex virus vaccine and pseudorabies virus vaccine (page 24, ll. 19 to 21) are read in the context of reporting work done by Lockhoff (USP 4,855,283) using glycolipid analogs as adjuvants, suggesting that such analogs could be used in the HMW-based composition as adjuvants. There is absolutely no suggestion in Barenkamp of "complexing additional composition to the immunogenic composition" in the form of herpes simplex virus (HSV), as asserted by the Examiner, but rather the possibility to use prior art glycolipid analogs as an adjuvant for the HMW protein is discussed since they have previously been used with HSV.

The references to tetanus toxoid and poliomyelitis virus vaccine (page 24, ll. 28 to 30) are in the context of reporting work performed by Maloney (USP 4,258,029) using octadecyl tyrosine hydrochloride (OTH) as adjuvants, suggesting that OTH could be used as an adjuvant in the HMW protein containing immunogenic compositions. There is absolutely no suggestion in Barenkamp of combining tetanus toxoid and/or polio vaccine with HMW in an immunogenic composition.

Similarly, the reference to hepatitis B virus antigen (page 24, ll. 31 to 32) is in the context of reporting work performed by Nixon-George et al (ref. 30) using octadecyl esters of aromatic amino acids as adjuvants, suggesting that such material would be used as adjuvants in the HMW protein containing immunogenic compositions. There is absolutely no suggestion in Barenkamp of combining hepatitis B virus antigen with HMW in an immunogenic composition.

It is submitted that it is entirely out of context to suggest, as the Examiner, that, on the basis of these disclosures, HMW protein would be combined with any one or a combination of herpes simplex virus vaccine, pseudorabies virus vaccine, tetanus toxoid, poliomyelitis virus vaccine and hepatitis B virus antigen in an immunogenic composition. The passages in question in Barenkamp et al are

discussing certain materials which may be used as adjuvants in the HMW-containing immunogenic composition, because they have been used in other vaccine formulations with the recited vaccine materials.

In the Appeal Brief, the applicants had questioned the source of the assertion that Barenkamp teaches that adhesin proteins are potentially important antigens which should comprise one component of a multicomponent non-typeable *H. influenzae* vaccination. In reply, the Examiner points to page 49, lines 15 to 19 of Barenkamp. It is submitted that this passage does not support the Examiner's assertion in that it states:

> "…. this data suggests that new HMW adhesin proteins are potentially important protective antigens which may comprise one component of a multicomponent NTHI vaccine" (emphasis added)

The permissive term "may" is used rather than the specific "should" used by the Examiner in the Answer. The words "may" and "should" do not mean the same thing.

The Examiner concedes in the Answer that:

> "….Barenkamp et al …, however, do not teach the use of a different antigen of *H. influenzae* which is not an adhesin in an immunogenic composition."

The Barenkamp reference suggests combining the HMW protein with other antigens, but does not reveal the identity of any such antigens. The Examiner is entirely incorrect to suggest that the passages on pages 24 to 25 in any manner suggest combining specific antigens with the HMW protein, but rather suggest the use of specific types of adjuvants with HMW, because they have been used with a variety of specifically-disclosed antigens.

The reference discloses the possibility, on page 49, of the provision of multicomponent NTHI vaccines of which HMW protein may be considered a candidate for inclusion. No other candidate for non-typeable *H. influenzae* antigens are described, but there is a suggestion that they should be adhesins. The Examiner is correct that Barenkamp does not teach the use of a different antigen of *Haemophilus influenzae* which is not an adhesin in an immunogenic composition with the HMW protein. In fact, as already seen, the Barenkamp et al reference is entirely silent as to any specific "at least one other immunogenic … material" which may be included in an immunogenic composition with the HMW protein.

In an attempt to remedy this defect, the Examiner turns to the Loosmore et al reference. It is possible largely to agree with the Examiner's statement in the Answer that:

> "Therefore, Loosmore et al., teach that it would be advantageous to provide analogs of Hin47 that are substantially reduced in proteolytic activity for use as an antigen or to be included in other immunogenic preparations (col. 2 lines 29-34). The isolated and purified adhesin analog has decreased protease activity which is less than about 10% of natural Hin47, yet still retains substantially the same immunogenic properties, where at least one amino acid contributing to protease activity may be deleted or replaced by a different amino acid to produce reduced activity (col. 2 lines 44-54). "The at least one deleted or replaced amino acid may be selected from amino acids 195-201 of Hin47, and specifically may be Serine-197, which may be deleted or replaced by alanine. In addition, the at least one deleted or replaced amino acid may be histidine-91 and may be deleted or replaced by alanine or lysine or arginine. Future, the at least one deleted or replaced amino acid may be Asparagine-121 and may be deleted or replaced by alanine or glutamic acid" (col. 2 lines 56-64). An immunogenic composition comprising an immuno-effective amount of Hin47 analog may be formulated as a vaccine for *in vivo* administration to a host; including a human to confer protection against diseases caused by a bacterial pathogen, such as *Haemophilus influenzae* (col. 3 lines 47-59)."

However, the Hin47 analog is not an adhesin.

The Examiner is correct that Loosmore et al contains the statement, paralleling the language in Barenkamp, that:

> "The immunogenic composition of the invention may further comprise at least one other immunogenic ..... material" (col. 3, ll 63 to 65)"

As in the case of Barenkamp, Loosmore et al is silent as to any other prospective other immunogenic material and certainly contains no specific reference to HMW proteins. The Loosmore et al reference does contain a little more information than Barenkamp with respect to multicomponent vaccines. In col. 9, lines 14 to 19, it is stated:

> "Vaccines which contain antigenic material as to several pathogens are combined vaccines and also belong to the present invention. Such combined vaccines contain, for example, material from various pathogens or from various strains of the same pathogen, or from combinations of various pathogens."

However, this passage contains no specific instructions of specific combinations of materials to be included in combined vaccines.

The statement by the Examiner in the Answer that:

> "The immunogenic composition ....may be contained within a live vector such as pox virus, salmonella, poliovirus, adenovirus, vaccinia or BCG (col. 3-4 lines 60-2)"

appears to make little sense. What is stated in col. 3, l. 66 to col. 4, line 2, is that the nucleic acid molecule comprising a gene encoding the Hin47 analog may be contained within a live vector. It is not seen of what relevance this statement has to an immunogenic composition comprising a combination of proteins.

While it is true as the Examiner states:

> "The analogs may be used as carrier proteins to make conjugate vaccines against antigenic determinants unrelated to Hin47 including pathogenic bacteria (col. 7 lines 15-18 and 40-51)."

It is not seen that this statement has any relevance to a composition comprising a mixture of proteins. The passage referred to by the Examiner simply states that the Hin47 analog can be used as a carrier protein in conjugate molecules with various bacterial pathogens. This statement has no relevance to a mixture of proteins.

Accordingly, neither the disclosure of Barenkamp nor the disclosure of Loosmore contains any disclosure to providing an immunogenic composition comprising the HMW protein disclosed in Barenkamp and the Hin47 analog disclosed by Loosmore. Each reference discloses the possibility of combining the specially-disclosed protein with other immunogenic compositions in an immunogenic composition but neither provides any suggestion to combine the two. It is only with the hindsight of the present invention that any link can be made with the two proteins.

The Examiner states in the Answer:

> "Therefore it would have been obvious at the time of appellant's invention to have an immunogenic composition to confer protection against *Haemophilus influenzae* comprising at least two different antigens, wherein one is a heat shock protein as taught by Loosmore et al., and the other is a high molecular weight adhesin protein, HMW1 or HMW2 which is an important protective antigen as taught by Barenkamp et al (WO 97/36914), because Loosmore et al, teaches

> that analogs of Hin47 with reduced protease activity from *Haemophilus influenzae* are useful in vaccination against disease caused by *H. influenzae* or other bacterial pathogens and these proteins are capable of eliciting protective opsonizing or bactericidal antibodies."

However, it is clear from the above analysis that there is no motivation provided by either Barenkamp or Loosmore et al to select the Hin47 analog of *Haemophilus influenzae* to combine with the HMW protein from the other potential known antigens of *Haemophilus influenzae*, for example, the P1, P2, P6 and D15 proteins, transferrin receptor proteins and lactoferrin receptor proteins.

In the Examiner's Answer, an attempt is made to address this issue. The Examiner states:

> "In response to appellant's argument that there is no suggestion to combine the references, the Examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art.
> However, it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose...[T]he idea of combining them flows logically from their having been individually taught in the prior art."

and then, omitting references to the case law the Examiner cites in support of the proposition, the Examiner states:

> "In this case, it would have been obvious at the time of appellant's invention to have an immunogenic composition to confer protection against *Haemophilus influenzae* comprising at least two different antigens, where one is a well known high molecular weight adhesin protein, HMW1 or HMW2, which are important protective antigens that should comprise one component of a multi-component non-typeable *H. influenzae* vaccine as taught by Barenkamp et al (WO 97/36914), in combination with the analog of Hin47 which is a non-proteolytic heat shock protein with substantially reduced proteolytic activity useable in other immunogenic preparation as taught by Loosmore et al."

First of all, as demonstrated previously, the Barenkamp reference does not state that the HMW protein <u>should</u> comprise one component of a multi-component, non-

typeable *H. influenzae* vaccinia but rather that it "may". There is no specific indication to combine the two specific antigens.

An important consideration in combining antigens, which may not be a factor when combining other types of materials, in the possibility of impairing or adversely affecting the respective immunogenicities of the antigens. In fact, applicants data showed antigenic interference for certain doses and an enhancing effect under other doses (see pages 12, line 13 to page 13, line 9). In addition, at dose levels where HMW and Hin47 proteins did not impair their respective immunogenicities, formulating such components with a DTP-polio-PRP-T vaccine did not result in any significant synergistic or suppressive effect on the additional antigen (see page 14, lines 10 to 23). Such results would not have been predicted in advance from the information provided in Barenkamp and Loosmore et al.

The Examiner states in the Answer with respect to this argument that:

> "In response to appellant's arguments, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious."

However, it is submitted that, from applicants data, this result does not, in fact, "flow naturally" from combining HMW protein and Hin47 protein. Rather, the respective quantities must be selected to avoid antigenic interference.

Accordingly, a person skilled in the art would not know ahead of time, assuming he were to select the non-proteolytic analog of Hin47 to combine with HMW, a motivation, it is submitted, which is completely lacking in the art, whether or not the proteins were combinable at all into an effective multi-component immunogenic composition. The idea of combining them does not flow logically from their having been individually taught in the prior art, contrary to the Examiner's suggestion.

The Examiner criticizes applicants discussion of the prior art, stating:

> "...one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references."

In order to analyze the teachings of the prior art, it is necessary first to analyze the teachings of each reference and the reliance that the Examiner makes on each of

the references and specific passages thereof in order to arrive at an objective assessment of the effect the teachings of one reference has on the other, to ascertain if the Examiner has made out a *prima facie* case of obviousness.

It is submitted that neither in the Appeal Brief nor in this Reply Brief, nor indeed at any stage of the prosecution, has applicant "attacked" the references individually. Rather applicants have made the analyses referred to above to demonstrate a lack of motivation to combine the references to arrive at applicants claimed composition.

The Examiner asserts in the Answer that:

> "No more than routine skill was required at the time of appellants invention to combine two well known antigens of *H. influenzae* an adhesin and a heat shock protein, since the prior art shows that both can elicit an immunogenic response in a host, both are useful to provide protection against a *H. influenzae* infection, both are useful in immunogenic composition in combination with other immunostimulating antigens. Accordingly, both are useful for the same purpose, to form an immunogenic composition to be used for that very same purpose. Appellant has provided no scientific data teaching away form the combination of two well known *H. influenzae* antigens."

It is not true, as the Examiner suggests, that both proteins function in the same way. First of all, the HMW protein only is present in about 75% of non-typeable strains and not at all in non-typeable strains. The HMW proteins are adhesin and function to prevent colonization. The Hin47 protein is present in non-typeable and typeable strains of *Haemophilus influenzae* but is not an adhesin. The proteins then function in different ways.

In addition to the non-proteolytic analog of Hin47, their are many other potential *Haemophilus influenzae* antigens which might be selected to combine with the HMW protein, assuming there were some motivation in the suggestion in the Barenkamp reference that other antigens may be present with the HMW protein (which, of course, the applicants assert does not exist). These proteins include the various outer membrane proteins, lactoferrin and transferrin receptor proteins and the D15 protein. There is no motivation provided by the cited prior art whereby a person skilled in the art, absent a knowledge of applicants claims, would specifically

select the non- proteolytic Hin47 analog among the wide choice available to combine with the HMW protein.

Accordingly, it is submitted that clams 6 to 24 are patentable over the applied combination of prior art and that the rejection of these claims under 35 USC 103(a) as being unpatentable over Barenkamp in view of Loosmore et al, should be REVERSED.

Respectfully submitted,

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